

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

ZEALAND PHARMA A/S
Smedeland 26B
DK-2600 Glostrup
DANEMARK

MODTAGET

26 JAN. 2004

kopi → Aventis
26/1 2004

Date of mailing (day/month/year)

15 January 2004 (15.01.2004)

Applicant's or agent's file reference

022-2003 WO1

IMPORTANT NOTICE

International application No.

PCT/DK2003/000463

International filing date (day/month/year)

02 July 2003 (02.07.2003)

Priority date (day/month/year)

04 July 2002 (04.07.2002)

Applicant

ZEALAND PHARMA A/S et al

1. Notice is hereby given that the International Bureau has **communicated**, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

AU, AZ, BY, CH, CN, CO, DE, DZ, EP, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BZ, CA, CR, CU, CZ, DK, DM, EA, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, SY, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 15 January 2004 (15.01.2004) under No. WO 2004/005342

4. **TIME LIMITS for filing a demand for international preliminary examination and for entry into the national phase**

The applicable time limit for entering the national phase will, **subject to what is said in the following paragraph**, be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of **19 months** from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, **time limits other than the 30-month time limit** will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For **regular updates on the applicable time limits** (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a **demand for international preliminary examination**, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

It is the applicant's **sole responsibility** to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Gijsbertus Beijer - Carlos Roy

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 338.91.11

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00463

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/575 C07K14/605 A61K38/26 A61P3/10 //C12N5/06,
A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K A61K C07D C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 43708 A (MADSEN KJELD ;NOVONORDISK AS (DK); HUUSFELDT PER OLAF (DK); KNUDSE) 2 September 1999 (1999-09-02) claim 89	1-78
X	WO 01 32158 A (SQUIBB BRISTOL MYERS CO ;PIPER BETH ANNE (US)) 10 May 2001 (2001-05-10) claim 69	1-78
X	US 6 358 924 B1 (HOFFMANN JAMES ARTHUR) 19 March 2002 (2002-03-19) claim 11	1-78
X	WO 01 04156 A (LARSEN BJARNE DUE ;NEVE SOEREN (DK); MIKKELSEN JENS DAMSGAARD (DK)) 18 January 2001 (2001-01-18) claims 1-48	1-78

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

30 September 2003

Date of mailing of the international search report

22 10. 2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

FERNANDO FARIETA /EÖ

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00463

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category ^a	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	EP 1 329 458 A (ZEALAND PHARMA AS) 23 July 2003 (2003-07-23) claim 6 ---	1-78
X	ANDREW A. YOUNG ET AL: "Studies in Obese Diabetic (ob/ob, db/db) Mice, Diabetic Fatty Zucker Rats, and Diabetic Rhesus Monkeys (Macaca mulatta)" DIABETES, vol. 48, May 1999 (1999-05), pages 1026-1034, XP002256109 figures 1,2 ---	1-78
X	LISA JUNTITI-BERGGREN ET AL: "The Antidiabetogenic Effect of GLP-1 Is Maintained During a 7-Day Treatment Period and Improves Diabetic Dyslipoproteinemia in NIDDM Patients" DIABETES CARE, vol. 19, no. 11, November 1996 (1996-11), pages 1200-1206, XP002256110 figure 1 ---	1-78
X	DAVID G. PARKES ET AL: "Insulinotropic Actions of Exendin-4 and Glucagon-Like Peptide-1 In Vivo and In Vitro " METABOLISM, vol. 50, no. 5, May 2001 (2001-05), pages 583-589, XP002256111 figure 2 ---	1-78
A	RÉMY BURCELIN ET AL: "Long-Lasting Antidiabetic Effect of a Dipeptidyl Peptidase IV-Resistant Analog of Glucagon-Like Peptide-1" METABOLISM, vol. 48, no. 2, February 1999 (1999-02), pages 252-258, XP002256112 figures 1,2 ---	1-78
A	U RITZEL ET AL: "A synthetic glucagon-like peptide-1 analog with improved plasma stability" JOURNAL OF ENDOCRINOLOGY, vol. 159, 1998, pages 93-102, XP002256113 figures 3,4 --- -/--	1-78

INTERNATIONAL SEARCH REPORT

Inter-Application No

PC 17UK 03/00463

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DORIS A. STOFFERS ET AL: "Insulinotropic Glucagon-Like Peptide 1 Agonists Stimulate Expression of Homeodomain Protein IDX-1 and Increase Islet Size in Mouse Pancreas " DIABETES, vol. 49, May 2000 (2000-05), pages 741-748, XP002256114 figure 3	1-78
A	US 6 344 180 B1 (HOLST J J ET AL) 5 February 2002 (2002-02-05) claims 1-13	1-78

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 03/00463

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-78
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 1-78

Claims 1-78 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practiced on the human or animal body (PCT Rule 39.1(iv)).

The wording "drug holiday" is defined (Description, page 11, lines 29-30) as the time interval between a first endpoint (start) and a second endpoint (finish). Claim 1 seems to comprise such definition by the wording "...without the continuous presence of the molecule".

According to W099/43708, the use of GLP-1 derivatives and exendin for the treatment of diabetes is known (See claim 89- W099/43708). Therefore, the term "drug holiday" appears to be unclear if it referring to the dose administrated, in that case the claims 40-78 comprise also therapy or diagnostic methods practiced on the human or animal body (PCT Rule 39.1(iv)).

Consequently, a search has been carried out for on the alleged effects of the compounds or compositions for GLP-1 derivatives and exendin. Further, the search has covered the general aspects of the invention to some extent, although it lacks the necessary precision in the definition of the subject matter due to the large quantity of material known within GLP-1 and exendin derivatives.

The search for the general concept of GLP-1 derivatives and exendin will retrieve a pertinent document only if this concept is described in general terms in a reference. Specific solutions previously known and falling under the general concept - but failing to mention this fact - are likely not to be revealed in such a search.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/UK 03/00463

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9943708	A	02-09-1999	AU 3247799 A 15-09-1999
		WO 9943708 A1	02-09-1999
		EP 1056775 A1	06-12-2000
		JP 2003522099 T	22-07-2003
		US 6268343 B1	31-07-2001
		US 2001011071 A1	02-08-2001
		US 2001047084 A1	29-11-2001
		ZA 9901571 A	02-09-1999
WO 0132158	A	10-05-2001	US 2002177602 A1 28-11-2002
		AU 1082601 A	14-05-2001
		AU 8022900 A	14-05-2001
		BG 106732 A	28-02-2003
		BG 106733 A	28-02-2003
		BR 0015294 A	15-07-2003
		BR 0015295 A	24-06-2003
		CA 2389928 A1	10-05-2001
		CA 2389931 A1	10-05-2001
		CN 1414862 T	30-04-2003
		CZ 20021547 A3	15-01-2003
		EP 1253944 A2	06-11-2002
		EP 1229918 A2	14-08-2002
		HU 0300218 A2	28-06-2003
		HU 0300642 A2	28-07-2003
		JP 2003519621 T	24-06-2003
		LT 2002062 A ,B	25-03-2003
		LT 2002063 A ,B	25-06-2003
		NO 20022086 A	24-06-2002
		NO 20022087 A	24-06-2002
		SK 4992002 A3	01-04-2003
		WO 0132157 A2	10-05-2001
		WO 0132158 A2	10-05-2001
		US 2002183345 A1	05-12-2002
US 6358924	B1	19-03-2002	AU 1617399 A 28-06-1999
		CA 2312190 A1	17-06-1999
		EP 1049486 A1	08-11-2000
		JP 2001525371 T	11-12-2001
		US 2002123466 A1	05-09-2002
		WO 9929336 A1	17-06-1999
WO 0104156	A	18-01-2001	EP 1076066 A1 14-02-2001
		AT 242267 T	15-06-2003
		AU 5966000 A	30-01-2001
		CA 2378431 A1	18-01-2001
		CN 1376166 T	23-10-2002
		DE 60003182 D1	10-07-2003
		WO 0104156 A1	18-01-2001
		EP 1196444 A1	17-04-2002
		EP 1329458 A2	23-07-2003
		JP 2003505347 T	12-02-2003
		NZ 517012 A	28-02-2003
		US 6528486 B1	04-03-2003
EP 1329458	A	23-07-2003	EP 1196444 A1 17-04-2002
		EP 1076066 A1	14-02-2001
		EP 1329458 A2	23-07-2003
		AT 242267 T	15-06-2003

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC1/DK 02/00463

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1329458	A	AU 5966000 A	30-01-2001
		CA 2378431 A1	18-01-2001
		CN 1376166 T	23-10-2002
		DE 60003182 D1	10-07-2003
		WO 0104156 A1	18-01-2001
		JP 2003505347 T	12-02-2003
		NZ 517012 A	28-02-2003
		US 6528486 B1	04-03-2003

US 6344180	B1 05-02-2002	AU 5489400 A	02-01-2001
		CA 2376473 A1	21-12-2000
		EP 1185308 A2	13-03-2002
		JP 2003502344 T	21-01-2003
		WO 0077039 A2	21-12-2000
		US 2003091507 A1	15-05-2003

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

☐ BLACK BORDERS

☒ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES

☐ FADED TEXT OR DRAWING

☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING

☐ SKEWED/SLANTED IMAGES

☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS

☐ GRAY SCALE DOCUMENTS

☐ LINES OR MARKS ON ORIGINAL DOCUMENT

☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY

☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.